II. REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Claims 47, 48, 50, 52-54 and 56-67 were pending and examined in the outstanding Office Action. In this Amendment and Reply, claims 47, 57, 63, 66 and 67 were amended. Claim 58 was canceled without prejudice. Claim 47 has been amended to correct a typographical error, i.e., to delete the word "of" and to amend the article related to the biological sample from "the" to "a" to provide antecedent basis for claim 67. Claim 57 was amended to include in the kit positive controls, negative controls and reagents and to remove the term "if present". This subject matter previously was recited in claim 58, now canceled. Claim 63 was amended to remove the Markush language since, as the Office noted, no Markush grouping is listed in the claim. Claim 66 was amended to correspond to claims 61 to 65, from which it depends. Claim 67 was amended to recite the specific type of liver cancer. Support for claim 67 is found in the specification on page 14, lines 2 and 3. Thus, the amendments to the claims and the addition of new claim 68 does not raise an issue of new matter and entry thereof is respectfully requested.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 47, 48, 50, 52-54, 56, 57 and 59-67 are pending in this application.

In view of the previous amendments and the remarks which follow, reconsideration and withdrawal of the objections and rejections is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claim 67 was rejected under 35 U.S.C. § 112, First Paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed

invention at the time the application was filed. The Office noted that this is a New Matter rejection. Without conceding the correctness of the Office's position and merely to advance examination of the application, claim 67 was amended to recite language taken verbatim from Applicants' specification. Accordingly, Applicants request that the new matter rejection be removed.

35 U.S.C. § 112, Second Paragraph

Claims 57-60, 61, 63, and 66 were rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office argued that the term "determining a genomic polymorphism" is vague because it can include a number of different functions such as amplifying, detecting sizes on a gel, etc. and it cannot be determined what specific function the "means" is drawn to.

Applicants respectfully traverse and note that means plus function claim language is permitted under 35 U.S.C. § 112, Paragraph 6 and the Office is required to look to Applicants' specification for structure corresponding to the claimed means. Applicants' specification on page 8, lines 11 to 14, page 14 and Figure 1 describes various structural means for determing if the polymorphism is present.

Claim 57 stands rejected on the ground that the term "if present" is vague and indefinite because it is not clear what the components of the kit would be if the polymorphism were not present. Without conceding the correctness of the Office's position and merely to advance examination, the rejected claim term was removed since its removal does not affect the claimed elements or scope.

Claim 61 was objected to for lacking antecedent basis for the tern "the subject's biological sample fluid" as there is no previous recitation to a biological sample fluid. Claim 47 has been amended herein to provide the antecedent basis for claim 61.

Claim 63 was objected to as indefinite as it contains Markush language "selected from the group consisting of" but the Office noted that there is no Markush Group set forth in the

claim. Claim 63 has been amended to remove the Markush language thereby removing the basis for the claim rejection.

Claim 66 also was rejected on the ground that the term "the extratumoral cells" lacks antecedent basis. Claim 66 has been amended to remove the language "extratumoral cells" and indicate that the subject's biological sample comprises normal cells.

Accordingly, in view of the preceding amendments and remarks, reconsideration and withdrawal of the objections and rejections are respectfully requested.

35 U.S.C. § 102

Claim 57 was rejected under 35 U.S.C. § 102(b) as allegedly anticipated by New England Biolabs Catalog (1996, page 102), for the reasons of record. Without repeating the basis for the rejection and without conceding the correctness of the Office's position, claim 57 has been amended to recite that the kit contains additional elements not present in the cited reference. In view of the aforementioned claim amendment, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 57-59 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Promega Catalog (19971, page 78 on the ground it teaches a kit comprising Taq DNA polymerase as a means for determining a genomic polymorphism at a tandemly repeated 28 base pair sequence.

Applicants maintain their position and respectfully traverse for the reasons of record.

35 U.S.C. § 103

Claims 57-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie in view Erlich (US Patent 5,468,613) and New England biolabs. The Office stated that Horie teaches a method for analyzing the number of repeats in the 5' UTR of the TS gene using PCR and size analysis on a gel (see page 192, col. 2-page 193; Figure 3). With regard to claim 57, the Office noted that the primers are considered means for determining a genomic

polymorphism in the TS 5' UTR. The Office further argued that the first primer taught by Horie is identical to instant SEQ ID NO: 6, and the 2nd primer of Horie "comprises" instant SEQ ID NO: 7 (contains 9 additional nucleotides on the *5'* end), which are the primers the specification teaches were used to "determine" the presence of the TS polymorphism. With regard to claims 58 and 59, the Office argued that Horie teaches using Taq polymerase, dNTPs, and reaction buffer for the PCR reaction, and further teaches analysis on a 4% agarose gel, the use of molecular markers for size analysis, as well as DNA tandemly repeated sequences (claim 60). The Office admitted that Horie does not teach packaging these means and reagents in kit format, but relied on Erlich to teach constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays and further that Erlich teaches providing kits which include reagents for identifying alleles in hybridization assay. The Office also argued that therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie, for determining the TS 5' UTR repeat alleles of a subject, in kit format, for the obvious improvement of providing the reagents in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The Office stated that the ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie more convenient to perform. The Office also stated that it would have been further obvious to provide either size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was co only used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. The Office further remarked that the use for the kit, the instructions in the kit and the temperature of the buffer solution carry no patentable weight as they does not provide any structural limitation to the kit.

Claims 47-48, 52-54, 56, 64 and 67 also were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman in view of Ruano.

The Office alleged that Horie teaches that triple tandemly repeated sequences are known

to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals. The Office also alleged that Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat as well as detection in leukocytes using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present. The Office stated that while Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility. The Office admitted that Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs.

The Office argued that however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene and that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. The Office alleged that Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Ruano is cited for allegedly teaching that genetic variability is a determinant of a patient's response to therapy and that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype. The Office also argued that Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences.

The Office argued that although Leichman does not teach that the expression of TS is

correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the *5'* regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to TS directed chemotherapy drugs. The Office further stated that an

> "ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create a prognostic test for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.
>
> Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5- FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to *5*-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer."

Claims 61-66 also were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47, 48, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The Office noted that the teachings of Horie and Leichman in view of Ruano are set forth supra and that Horie and Leichman in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

The Office cited Howells for teaching a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. The Office argued that Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood or tissue identified as macroscopically normal by the surgeon for genotyping. Howells is cited for further teaching that null alleles for both GSTTl and GSTM1 was associated with nonresponsiveness to chemotherapy.

Govindarajan is cited for teaching a method using PCR to genotype the GSTMl gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan also is cited for allegedly teaching that there was a higher incidence of GSTMl null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

The Office argued that both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug. The Office further stated that although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie is cited for teaching that the number of repeats is associated with TS expression in normal cells and therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

The Office opined that given that Leichman teaches that expression levels of TS

correlated with sensitivity to 5- FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals, 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, and 4) TS genotype could be determined for a subject from normal cells, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

Claims 57-60 also were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of Erlich (US Patent 5,468,613) and New England biolabs.

The Office applied the assertions of Horie and Leichman in view of Ruano are set forth above. The Office admitted that Horie and Leichman, in view of Ruano, do not teach a kit comprising means for determining TS 5' UTR genotype or DNA tandemly repeated sequence of the TS gene but relied on Erlich for allegedly teaching constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays. The Office argued that Erlich teaches providing kits which include such sequence specific oligonucleotides and that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie for use in the method of Horie and Leichman in view of Ruano, for determining the TS 5' UTR repeat alleles of a subject, in kit format, for the obvious improvement of providing the reagents in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The Office stated that the ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the

method of Horie and Leichman in view of Ruano more convenient to perform. The Office also argued that it would have been further obvious to provide size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was co only used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that the use for the kit and the instructions in the kit carry no patentable weight. It was further argued by the Office that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Applicants respectfully traverse and incorporate by reference the reasons of record why the Office has failed to present a prima facie case of obviousness. Applicants also direct the Office's attention to the attached declaration of one of skill in the field of the claimed invention. Dr. Danenberg states in his declaration that, contrary to Office's position, the invention of the claims would not have been obvious to one of skill in the art to screen for the polymorphism in the 5' UTR of the TS gene and correlate the results to sensitivity and/or responsiveness to a particular therapeutic regimen. In view of the prior remarks and the attached Declaration of Dr. Danenberg, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper

or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: July 27, 2006

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